

day 4, and either wild-type or resistant virus was observed at day 8 in 4 of 8 patients with HCV RNA levels above the LLD. Viral levels continued to decline in all patients. All 8 patients began standard therapy (peg-IFN/RBV) and their HCV RNA levels were undetectable 3 months after the 14-day study period. Among patients dosed with telaprevir alone, four patients had a breakthrough or plateau response. In these patients, R155 and A156V/T variants were detectable by day 8, and the V36(M/A)/R155(K/T) variant predominated by day 14. Four other patients dosed with telaprevir alone all had a continuous decline in HCV RNA levels. Two of these patients had A156V/T uncovered by day 8, while the other two had levels below LLD. Conclusions: The rapid and dramatic antiviral response to telaprevir reflects a sharp reduction in wild-type virus. Viral variants were uncovered as wild-type virus was cleared. HCV RNA levels can decline in patients receiving telaprevir monotherapy, even in those with detectable A156V/T variant. Viral rebound with monotherapy appears to result from the presence of V36(M/A)/R155(K/T); this could be due to greater fitness of this variant compared to A156V/T. The combination of telaprevir and peg-IFN suppressed resistant variants, indicating that these variants are fully sensitive to peg-IFN.

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VALOPICITABINE (NM283) PLUS PEG-INTERFERON IN TREATMENT-NAÏVE HEPATITIS C PATIENTS WITH HCV GENOTYPE-1 INFECTION: HCV RNA CLEARANCE DURING 24 WEEKS OF TREATMENT Eric Lawitz¹, Tuan Nguyen², Ziad Younes³, John Santoro⁴, Norman Gitlin⁵, David McEniry⁶, Richard Chasen⁷, John Goff⁸, Steven Knox⁹, Kristin Kleber⁹, Bruce Belanger⁹, Nathaniel A. Brown⁹, Douglas Dieterich¹⁰, Investigator Group The 006⁹; ¹Alamo Medical Research, San Antonio, TX; ²Tuan Nguyen, M.D., San Diego, CA; ³Gastroenterology Center of the Mid-South, Germantown, TX; ⁴AGA Clinical Research Assoc., Egg Harbor, NJ; ⁵Atlanta Gastroenterology Associates/Emory University, Atlanta, GA; ⁶Northwest Medical Specialties, Tacoma, WA; ⁷Maryland Digestive Disease Research, Laurel, MD; ⁸Rocky Mountain Gastroenterology, Lakewood, CO; ⁹Idenix Pharmaceuticals, Cambridge, MA; ¹⁰Mt. Sinai School of Medicine, New York, NY

Background: Valopicitabine (NM283) showed dose-related anti-HCV activity, alone and combined with pegylated interferon (NM283/pegIFN) in trials of patients with hepatitis C (HCV genotype 1). In this ongoing Phase IIb trial, Week 4 (W4) data from treatment-naïve patients showed significantly greater HCV RNA reductions with NM283/pegIFN compared to pegIFN alone (Dieterich, EASL 2006). Here we report longer term results from this trial. **Methods:** Enrolled pts have hepatitis C (HCV-1), HCV RNA $\geq 5 \log_{10}$ IU/mL by TaqMan™ PCR, ALT $< 5 \times$ ULN, compensated liver disease, and no prior treatment. Pts were randomized into 5 treatment groups: (A) pegIFN alone QW to W4, with NM283 added in W5 (dose ramped from 400 to 800 mg/d), with both drugs continued thereafter (B) NM283 200 mg/d + pegIFN (C) NM283 ramped 400 to 800 mg/d in 1st wk, + pegIFN (D) NM283 800 mg/d, + pegIFN (E) NM283 800 mg/d, + pegIFN. PegIFN- $\alpha 2a$ is dosed 180 μ g QW starting Day 8 (Groups A-D) or Day 1 (Group E). Serum HCV RNA is assessed by the TaqMan™ real-time PCR assay, with PCR-nondetectability reported here at the historically-

used Amplicor™ PCR quantitation limit and the TaqMan™ limit. **Results:** The study is fully enrolled with 173 pts. Final W12 HCV RNA results and interim W24 results (with data presently available for 96/173 pts) are shown below. Compared to prior W4 results, W12 and W24 data show a convergence of anti-HCV efficacy across treatment groups due to continued viral clearance to PCR-nondetectable levels in most pts in all groups. Early virologic response ($\geq 2 \log_{10}$ drop in HCV RNA at W12) was observed in 82-92% of pts. Treatment B (with NM283 200 mg/d) has been generally well-tolerated. GI side effects were more common and were occasionally severe at the 800 mg/d NM283 dosing level (arms C-E). After a protocol amendment pts are continuing NM283 at the 200 or 400 mg/d levels (with weekly pegIFN) with improved tolerance to date. Final W24 results will be available at the meeting. **Conclusions:** At doses as low as 200 mg/d, valopicitabine plus pegIFN markedly suppresses viremia in treatment-naïve patients with HCV-1 infection. By W24, most patients have achieved PCR-nondetectable HCV RNA by the sensitive TaqMan assay.

Treatment Group	Mean \downarrow from Baseline (log ₁₀ IU/mL)				Amplicor™ negative <600 IU/mL (%)		TaqMan™ negative <20 IU/mL (%)	
	n	Week 12	n	Week 24	Week 12	Week 24	Week 12	Week 24
A	34	-4.11	18	-4.50	68	83	59	61
B	34	-3.86	20	-4.44	68	75	44	70
C	34	-4.11	20	-4.48	74	80	44	65
D	36	-4.57	18	-4.71	81	83	67	72
E	35	-4.04	20	-4.06	69	60	54	50

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INHIBITORY ACTIVITY OF THE 2,4-DIAMINO-6-[2-(PHOSPHONOMETHOXY)ETHOXY]-PYRIMIDINE (PMEO) AGAINST WILD TYPE AND DRUG RESISTANT MUTANTS OF HBV Marie-Noelle Brunelle¹, Julie Lucifora¹, Stephanie Villet¹, Johan Neyts², Christian Trepo¹, Fabien Zoulim¹; ¹INSERM U271, Lyon, France; ²Rega institute for Medical Research, Leuven, Belgium

Background/Aim. Successive anti-human hepatitis B virus (HBV) therapy with nucleoside analogs leads to the emergence of resistant HBV strains harboring complex pattern of mutations within HBV polymerase gene. The development of new HBV inhibitors is thus needed. The 2,4-diamino-6-[2-(phosphonomethoxy)ethoxy]-pyrimidine (PMEO), a novel acyclic pyrimidine nucleoside phosphonate analog, was shown to have an anti-HBV effect comparable to adefovir (ADV) in hepatoma cells expressing permanently wild-type (wt) or lamivudine-resistant (LAM-R) HBV. In this study, we investigated the cross-resistance profile of multiple-resistant HBV strains against PMEO in comparison to LAM, ADV, entecavir (ETV) and tenofovir (TDF). **Methods.** The anti-HBV activity of the drugs was evaluated after transfection of Huh7 cells with HBV genomes cloned in a pTriex-HBV vector. These genomes are from a) laboratory HBV strains [wt, LAM-R (L180M/M204V), ADV-R (N236T) or LAM+ADV-R (L180M/M204V/N236T)], b) the viral quasispecies of a chronically infected patient failing successive therapy with LAM and LAM+ADV (patient 1) [wt, LAM-R (L180M/M204V; L180M/A181V) or LAM+ADV-R (V173L/L180M/A181V; V173L/L180M/A181V/M204V; V173L/L180M/A181V/N236T; V173L/L180M/A181V/M204V/N236T)], c) a chronically infected patient failing successive therapy with LAM and ETV (patient 2) [wt, LAM-R (V173L/L180M/M204V) or ETV-R (L180M/M204V/S202G)]. Drugs were administered daily from day 4 to day 9 post transfection. Cells were lysed at day 9 for analysis of intracellular viral DNA by Southern Blot hybridization.